Bifurcation stenting with drug-eluting stents: a systematic review and meta-analysis of randomised trials

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CRD summary
This generally well-conducted review concluded, although rates of death, stent thrombosis and restenosis were similar between patients undergoing bifurcation stenting with drug-eluting stents, myocardial infarction was more common with a two-stent strategy; provisional stenting should be the primary strategy. However, in the absence of a significant effect on mortality, the authors’ conclusions and recommendations for practice may be overstated.

Authors' objectives
To determine if outcomes differ between provisional stenting (elective side-branch or T-stenting) compared with routine two-stent strategy (mandatory side-branch stenting) for the treatment of bifurcation stenoses of the coronary arteries using drug-eluting stents.

Searching
EMBASE, MEDLINE, and the Cochrane Library were searched from January 2000 to February 2009 for articles in any language. Search terms were reported. Conference proceedings from five professional bodies were searched, along with two relevant websites. Reference lists of relevant reviews were scanned.

Study selection
Randomised controlled trials (RCTs) that compared provisional drug-eluting stent versus two drug-eluting stent strategies for the treatment of bifurcation stenoses in patients with coronary artery disease were eligible for inclusion. Trials had to report the rate of restenosis. Patients were allowed to receive clopidogrel treatment.

Outcomes were mortality, myocardial infarction, target lesion revascularisation, and stent thrombosis.

The included trials compared provisional sirolimus or paclitaxel drug-eluting stents versus sirolimus or paclitaxel drug-eluting two-stent strategy for the treatment of bifurcation lesions. The mean age of included patients ranged from 60 to 67 years; most of the patients were male (77 to 81%). All patients received clopidogrel treatment for three to 12 months.

Two reviewers performed study selection.

Assessment of study quality
Quality assessment was conducted using a risk of bias table, which assessed sequence generation, allocation concealment, blinding, incomplete outcome data assessed, selective reporting, and other biases. Each quality item was scored as low risk of bias, unclear risk of bias, or high risk of bias.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Two reviewers independently extracted data on mortality, myocardial infarction, target lesion revascularisation, restenosis and thrombosis. Data were used to calculate relative risks (RRs) and 95% confidence intervals (CIs). Where possible, intention-to-treat data were used.

Methods of synthesis
The pooled relative risks were calculated using a Mantel-Haenszel fixed-effects meta-analysis, when no statistical heterogeneity was detected; a random-effect meta-analysis was used when statistical heterogeneity was detected.

Statistical heterogeneity was assessed using the $I^2$ statistic and Cochrane Q test. The absolute risk difference (RD) and
number needed to treat were calculated when the pooled relative risk was statistically significant. Statistical heterogeneity was explored using meta-regression.

Sensitivity analyses were undertaken to explore the effects of trial quality and trial factors such as trial size and bifurcation type.

Publication bias was assessed using funnel plot analysis, Egger's linear regression and Begg and Mazumdar rank correlation; it was explored using Duval and Tweedie’s trim-and-fill method.

**Results of the review**

Six RCTs were included in the review (n=1,641 patients). The sample size of the included trials ranged from 85 to 500 patients. Trial quality assessment indicated that for many quality factors there was a low risk of bias, but for blinding there was high to uncertain risk of bias.

Compared with the two drug-eluting stent strategy, provisional drug-eluting stenting had a statistically significant lower risk of myocardial infarction (RR 0.57, 95% CI 0.37 to 0.87; $I^2=13\%$), which equated to a pooled risk difference of -3.0% (95% CI -1.0% to -5.0%); the number needed to treat to prevent one myocardial infarction using the provisional strategy was 33 patients. There was no statistically significant difference between the two-stent strategy and the provisional strategy for mortality, target lesion revascularisation, main-branch stenosis, side-branch stenosis, or stent thrombosis.

Sensitivity analyses indicated that larger trials, multicentre studies, and longer follow-up periods were more likely to show an increase in myocardial infarction with the two-stent strategy.

There was no evidence of publication bias.

**Authors' conclusions**

The use of a one-stent strategy with provisional T-stenting of the side branch yielded similar rates of death, restenosis and stent thrombosis compared with a two-stent strategy; provisional drug-eluting T-stenting should be considered the primary strategy for bifurcation stenoses.

**CRD commentary**

Inclusion criteria for the review were clearly defined. Several relevant databases were searched for articles in any language. Publication bias assessed and was not detected. Study selection and data extraction were conducted in duplicate to attempt to minimise error and bias, but it was unclear if the same process was used for quality assessment.

Quality assessment was based on a simple checklist of trial biases, which may not give a true reflection of trial quality. Trials were pooled using a fixed-effects or random-effects meta-analysis, depending on the presence of statistical heterogeneity. Sensitivity analyses were undertaken, which was appropriate. The results of the review demonstrated only one real difference between the two treatment strategies, so the authors’ conclusion that provisional stenting should be used as the primary strategy was not fully supported by the data.

The review was generally well conducted but, in the absence of a significant effect on mortality, the authors’ conclusions and recommendations for practice may be overstated.

Three authors disclosed financial links with Abbott, Boston Scientific, Cordis and/or Medtronic (all manufacturers of drug-eluting stents).

**Implications of the review for practice and research**

**Practice**: The authors stated that provisional T-stenting should be considered the primary strategy for bifurcation stenoses when anatomically suitable, with crossover to a two-stent strategy when necessary.

**Research**: The authors stated that further research is needed beyond one-year and after discontinuation of clopidogrel.
Research is also needed to assess whether a final kissing balloon inflation is needed after provisional stenting.

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